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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ROBINSON, BINTA M	

ART UNIT	PAPER NUMBER
1625	

DATE MAILED: 06/04/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/854,694	JENSEN ET AL.	
	Examiner	Art Unit	
	Binta M. Robinson	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,6,7,9,10,14,15,24 and 25* is/are pending in the application.

4a) Of the above claim(s) *7 and 10* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,6,9,14,15,24 and 25* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Detailed Action

Claims 1-2, 6, 7, 9, 10, 14, 15, 24, and 25 are pending in the case. The Group I invention elected at paper no. 11 to the compound of formula I, where A and B are –(Ch2)n, where n is 0 or 1, R2 is pyridyl optionally substituted as claimed in the claim amendments dated 2/17/04, R1 is a carbocyclic ring as claimed which is Phenyl or benzyl, R' and R" are as claimed in the claimed claim amendments dated 2/17/04, R3 and R4 are as claimed in claim amendments dated 2/17/04.

The applicant traverses the restriction requirement, allleging that all of the compounds of the invention share a common utility as SK/IK/BK ion channel modulating agents. The applicant also asserts that the core of the molecue is essentially common such that when A and B are restricted to (CH2)0-5, then R1-R4 should not be restricted. However, US Patent 6204277 discloses compound 2, 4-Pentanedione, 3-methyl-3-[[4-[2-(5-methyl-2-phenyl-4-oxazolyl)ethoxy]phenyl]methyl] as being a blood sugar lower agent, but makes no reference to this compound lower blood sugar by modulating any ion channels. Additonally, the art shows that when R1 is phenyl and R2 is OH, then the compounds do not have any therapeutic use, but are synthetic preparations. See 2,4-Hexanedione, 3-hydroxy-3-(phenylmethyl)- in Tetrahedron (1996), 52 (16), 5799-804. Thus the restriction is justified, because the utility of the compound changes when R1-R4 are varied.

This Restriction is FINAL. Claims 7, 10, 14 are withdrawn from further consideration as being drawn to nonelected subject matter.

The 112, first paragraph scope of enablement rejection of claims 1, 2, 4, 5, 6, 8, 9, 15, 24-25 of R2 and R3 and R4 radicals of the compound of formula I is withdrawn in light of applicant's remarks in the amendment dated 2/17/04. The 112, first paragraph rejections of the diseases in claims 24 and 25 are maintained and clarified.

(modified rejections)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 24-25 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. There is insufficient description for a method of treatment or alleviation of any disease or disorder or a condition of a living animal, including a human, which disorder or disease or condition is responsive to modulation of Skca, Ikca and/or BKCa channels, comprising the step of administering to such a living animal body, in need thereof a therapeutically effective amount of the instant compounds of claim 1. There is also insufficient description of whether or not modulating these Skca, Ikca and/or BKCa channels is sufficient to the treat the diseases claimed in claim 25. There is also insufficient description of derivatives, hydrates being claimed in claims 1 and 2. In the absence of how to make the hydrate and derivatives

being claimed, there is no umbrella coverage springing forth from the claimed compound and the absence of examples of derivatives and hydrates.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. 112, first paragraph, have need described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and
8. the level of the skill in the art.

The nature of the Invention

The nature of the invention is the use of the instant compounds in claim 1 as ion channel modulating agents.

The state of the prior art

Ion channels are a large family of related proteins representing 1% of human genetic endowment. Ion channels carry out no biochemical transformations since the product and substrate are inorganic ions and differ only in regard to the side of the membrane on which they reside. Ion-channel diseases reflect a relatively new category of inborn error and were first recognized in 1989, with the isolation of cystic fibrosis transmembrane conductance regulator. Ion –channel disorders are thought to cause pathology in virtually every organ system. Although cystic fibrosis is historically the first recognized genetic ion-channel disease, it remains one of the least understood. See Gargus. Some of the diseases claimed by applicants can be caused by other pathways in addition to defective ion channels and it may be difficult to design one drug that can

specifically treat diseases as wide ranging as diarrhea and cystic Fibrosis at the same time. For example, the wide range of Cystic Fibrosis phenotypes have been shown to result from modifications in inflammatory and anti-inflammatory mediators genes, genes for antioxidants, mediators of airway reactivity, antinflammatory mediators as well as alternative ion channels. (See Journal of Laboratory and Clinical Medicine (2003) – Ca 139:82785. The fact that diarrhea is caused by a wide range of toxins, acting via different mechanisms at different epithelial cell membranes, makes it difficult to design a target-specific vaccine against toxin-induced diarrhea for example. Diverse strategies, depending on the toxin's mechanism of action, are required to combat toxin-induced diarrhea. (Se Laohachai et. Al.)

The predictability or lack thereof in the art

The instant claimed invention is highly unpredictable as discussed below:

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. In re Fisher, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the instant claimed invention is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of ion channel-mediated diseases, whether the specific ion channel was activated or inhibited would affect the possible treatment of any disease.

Hence, in the absence of a showing of correlation between all the diseases claimed as capable of treatment by the compound of claim 1 and the inhibition or activation of Skca, Ikca and/or BKCa channels , one of skill in the art is unable to fully predict possible results from the administration of the compound of claim 1 due to the unpredictability of the role of ion channels, i.e. whether activation or inhibition of these ion channels would be beneficial for the treatment of the diseases. For example, As Lahohachai points, out some of the diseases claimed, such as diarrhea, can be caused by diverse mechanisms of action and will require diverse drug strategies of treatment depending on the mechanism of action.

The nature of pharmaceutical arts is that it involves screening *in vitro* and *in vivo* to determine which compounds exhibit the desired pharmacological activities. There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

The amount of direction or guidance present

The direction present in the instant specification is that the compounds of claim 1 can modulate Skca, Ikca and/or BKCa channels , which helps in the treatment of the claimed diseases. However, the specification is silent and fails to provide guidance as to whether the diseases listed as Skca, Ikca and/or BKCa channel - mediated diseases, require the activation or inhibition of Skca, Ikca and/or BKCa channels for treatment, - in Fact, the prior art indicates that diseases such as Diarrhea, are not singularly caused

by ion channel defects, but can be caused by other mechanisms of action, which may require therapies alternative to ion channel therapies i.e. the specification fails to provide a correlation between the diseases listed and the activation or inhibition of Skca, Ikca and/or BKCa ion channels.. The specification discloses that all of the test compounds showed activity at a final concentration of about 10 microMoles, and that these compounds are there SK/IK/BK channel modulating agents. However, the specification does not go into how effective these compounds are in modulating these channels.

The presence or absence of working examples

The specification discloses that all of the test compounds showed activity at a final concentration of about 10 microMoles, and that these compounds are there SK/IK/BK channel modulating agents. However, the specification does not go into how effective these compounds are in modulating these channels.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine what listed diseases would be benefited by the activation or inhibition of ion channels would furthermore then have to determine whether the claimed compounds would provide treatment of the disease by the inhibition or activation of these channels.

The level of Skill in the art

The level of skill in the art is high. However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be

individually assessed for physiological activity by in vitro and in vivo screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the claim 1 for the treatment of an ion channel-mediated diseases. As a result necessitating one of skill to perform an exhaustive search for which ion channel-mediated diseases can be treated by the compound of claim 1 in order to practice the claimed invention.

Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001 , states that " a patent is not a hunting license. It is not a reward for search , but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and In re Fisher (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which ion channel-mediated diseases can be treated by the compound encompassed in the instant claims, with no assurance of success.

New Rejections

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim(s) 1, 2, 6, 9, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Sammes et. al. Sammes discloses the instant compounds e and m. At page 2835 , see the instant compounds e and m.

If the applicant does not narrow the claims to the elected examined subject matter, 103 (a) rejections will be made over compounds b, c, d, j, k, l, n, and o, at page 2835 of this reference.

Claim(s) 1, 2, 6, and 15 are rejected under 35 U.S.C. 102(b) as being anticipated by Umemoto et. al. discloses the instant compounds 38, 39, and 40. At page 8568, see the instant compounds.

Claim(s) 1, 2, 6, and 9 are rejected under 35 U.S.C. 102(b) as being anticipated by Mohrbacher et. al. discloses the instant compound dimethyl phenyl 2-pyridylmethylmalonate, line 26. At page 8568, see the instant compounds. If applicants do not narrow the claims to the elected subject matter, claim s 1, 2, 6, and 9 can also be rejected over the compound diethyl 2- pyridylmethylenemalonate at column 3, line 71.

Claim(s) 1, 2 and 6 are rejected under 35 U.S.C. 102(b) as being anticipated by Kaneko et. al. discloses the instant compound 149. At page 828, see the instant compound.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, and 6 are rejected under 35 U. S. C. 103(a) as being unpatentable over Kaneko. Kaneko et. al. teaches the instant compound, 149. At page 828, see the instant compound. Kaneko also discloses the reactant compounds, pyridine, 2-bromo; pyridine, 2-methyl; pyridine, 2-chloro; 4-pyridineamine; 3-pyridinamine; 2-pyridiname; pyridine, 3-bromo which are reactants used to make the intermediate compound, 149. See Ca 128:204878.

The difference between the prior art compound and the instantly claimed compounds is the teaching of a generic compound versus a disclosed species. The instant claims generically claim propanedioic acid, (2-pyridinyl) phenyl, diethyl ester compounds that can be substituted on the pyridinyl ring by nitro, alkyl, amino, or halo whereas the prior art reference discloses the starting materials that can produce these species intermediates, such as propanedioic acid, (5-nitro-2-pyridinyl)phenyl, diethyl ester which is substituted with nitro on the phenyl ring as well as one of the species intermediates produced by these starting materials, which is compound 149. It would have been obvious to one of ordinary skill in the art to select various known radicals within a genus to prepare structurally similar compounds and to prepare intermediates substituted on the pyridyl ring of the compound with nitro, alkyl, amino or halo from the disclosed starting materials. For instance, see the compound 149, where a disclosed

species is exemplified. Accordingly, the compounds are deemed unpatentable therefrom in the absence of a showing of unexpected results for the claimed compounds over those of the generic prior art compounds.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Binta M. Robinson whose telephone number is (571) 272-0692. The examiner can normally be reached on M-F (9:30-6:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph McKane can be reached on 571-272-0699.

A facsimile center has been established. The hours of operation are Monday through Friday, 8:45 AM to 4:45 PM. The telecopier numbers for accessing the facsimile machine are (703)308-4242, (703)305-3592, and (703)305-3014.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571)-272-1600.

BMR
May 11, 2004

JOSEPH K. McKANE
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600